



EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the substantiation of a health claim related to Pacran® and defence against bacterial pathogens in the lower urinary tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006

EFSA Publication

Link to article, DOI:
[10.2903/j.efsa.2014.3656](https://doi.org/10.2903/j.efsa.2014.3656)

Publication date:
2014

Document Version
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Citation (APA):
EFSA Publication (2014). *EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the substantiation of a health claim related to Pacran® and defence against bacterial pathogens in the lower urinary tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006*. European Food Safety Authority. the EFSA Journal Vol. 12(5) No. 3656 <https://doi.org/10.2903/j.efsa.2014.3656>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

SCIENTIFIC OPINION

Scientific Opinion on the substantiation of a health claim related to Pacran® and defence against bacterial pathogens in the lower urinary tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2,3}

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

Following an application from Naturex SA, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to Pacran® and defence against bacterial pathogens in the lower urinary tract. The food that is the subject of the claim is Pacran®. The Panel considers that the food, Pacran®, which is the subject of the claim is sufficiently characterised in relation to the claimed effect. The Panel considers that defence against bacterial pathogens in the lower urinary tract is a beneficial physiological effect. One human study from which conclusions could be drawn for the scientific substantiation of the claim showed no effect of Pacran® on defence against bacterial pathogens in the lower urinary tract. The Panel concludes that a cause and effect relationship has not been established between the consumption of Pacran® and defence against bacterial pathogens in the lower urinary tract.

© European Food Safety Authority, 2014

KEY WORDS

Pacran®, proanthocyanidins, cranberry, *Vaccinium macrocarpon*, urinary tract, health claims

¹ On request from the Competent Authority of France following an application by Naturex SA, Question No EFSA-Q-2013-00889, adopted on 10 April 2014.

² Panel members: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen. Correspondence: nda@efsa.europa.eu

³ Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Sean (J.J.) Strain, Inge Tetens, Hendrik van Loveren, Hans Verhagen and Peter Willatts for the preparatory work on this scientific opinion.

Suggested citation: EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the substantiation of a health claim related to Pacran® and defence against bacterial pathogens in the lower urinary tract pursuant to Article 13(5) of Regulation (EC) No 1924/2006. EFSA Journal 2014;12(5):3656, 11 pp. doi:10.2903/j.efsa.2014.3656

Available online: www.efsa.europa.eu/efsajournal

SUMMARY

Following an application from Naturex SA, submitted pursuant to Article 13(5) of Regulation (EC) No 1924/2006 via the Competent Authority of France, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the scientific substantiation of a health claim related to Pacran® and defence against bacterial pathogens in the lower urinary tract.

The scope of the application was proposed to fall under a health claim based on newly developed scientific evidence. The application includes a request for the protection of proprietary data.

The food that is the subject of the health claim is Pacran®, which contains cranberry powder obtained from the blend of whole North American cranberries (*Vaccinium macrocarpon*, syn. *V. macrocarpon* Aiton or *V. macrocarpon* L). The applicant claims that proanthocyanidins (PACs) are the main food constituent in the Pacran® which are responsible for the claimed effect. The Panel considers that the food, Pacran®, which is the subject of the health claim is sufficiently characterised in relation to the claimed effect.

The claimed effect proposed by the applicant is “helps to inhibit the adhesion of P-fimbriated *Escherichia coli* to the urinary tract cells”. The target population proposed by the applicant is “sexually active women with a history of UTIs”. The Panel considers that the claimed effect refers to defence against bacterial pathogens in the lower urinary tract in healthy women without signs or symptoms of a urinary tract infection (UTI) and does not include the treatment of UTI. The Panel considers that defence against bacterial pathogens in the lower urinary tract is a beneficial physiological effect.

The applicant identified four studies as pertinent to the claim: two human intervention studies and two *ex vivo* studies. The Panel considers that no conclusions can be drawn from one of the human studies for the scientific substantiation of the claim and that the second human study had design limitations but did not show an effect of Pacran® on defence against bacterial pathogens in the lower urinary tract.

In addition, the applicant provided two studies on the *ex vivo* anti-adherence properties of urine from subjects consuming Pacran® on uropathogenic *E. coli* strains as being pertinent to the claim. The Panel considers that these studies do not provide evidence that an inhibition of the adhesion of *E. coli* to uroepithelial cells by urine from subjects consuming Pacran® is predictive of the occurrence of a clinically relevant inhibition of the adhesion of *E. coli* to uroepithelial cells in humans.

On the basis of the data presented, the Panel concludes that a cause and effect relationship has not been established between the consumption of Pacran® and defence against bacterial pathogens in the lower urinary tract.

TABLE OF CONTENTS

Abstract	1
Summary	2
Table of contents	3
Background	4
Terms of reference.....	4
EFSA Disclaimer.....	4
Information provided by the applicant	6
Assessment	6
1. Characterisation of the food	6
2. Relevance of the claimed effect to human health.....	7
3. Scientific substantiation of the claimed effect.....	7
Conclusions	8
Documentation provided to EFSA	9
References	9
Abbreviations	11

BACKGROUND

Regulation (EC) No 1924/2006⁴ harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation, and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Article 13(5) of this Regulation lays down provisions for the addition of claims (other than those referring to the reduction of disease risk and to children's development and health) which are based on newly developed scientific evidence, or which include a request for the protection of proprietary data, to the Community list of permitted claims referred to in Article 13(3).

According to Article 18 of this Regulation, an application for inclusion in the Community list of permitted claims referred to in Article 13(3) shall be submitted by the applicant to the national competent authority of a Member State, which will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 11/11/2013.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction.
- The scientific evaluation procedure started on 4/12/2013.
- On 22/01/2014, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application, and the clock was stopped on 29/01/2014, in compliance with Art. 18(3) of Regulation (EC) No 1924/2006.
- On 13/02/2014, EFSA received the requested information as submitted by the applicant and the clock was restarted.
- During its meeting on 10/04/2014, the NDA Panel, having evaluated the data submitted, adopted an opinion on the scientific substantiation of a health claim related to Pacran® and defence against bacterial pathogens in the lower urinary tract.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 16(3) of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the scientific substantiation of a health claim related to Pacran® and defence against bacterial pathogens in the lower urinary tract.

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation for the marketing of Pacran®, a positive assessment of its safety, nor a decision on whether Pacran® is, or is not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

⁴ Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 18(4) of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: Naturex SA, Site d'Agroparc, BP 1218, 84911, Avignon cedex 9, France.

The application contains a request for the protection of proprietary data for manufacturing process and three unpublished studies in accordance with Article 21 of Regulation (EC) No 1924/2006.

Food as stated by the applicant

According to the applicant, the food for which this health claim is made is Pacran®, which is a proanthocyanidins (PAC) standardised cranberry powder derived from a proprietary blend of whole North American cranberries (*Vaccinium macrocarpon* Aiton of the botanical family Ericaceae). The PAC content and the ratio of PAC type A were specified.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect is the inhibition of the adhesion of P-fimbriated *E. coli* to urinary tract cells. PACs, in particular the A-type linkages, are similar in structure to the bacteria-binding receptors found on the surface of uroepithelial cells. Thus, PACs bind to bacterial fimbriae and have been implicated in the competitive inhibition of P-fimbriated *E. coli* adhesions to uroepithelial cell surface receptors, *in vitro* and *ex vivo*. This mechanism facilitates the reduction of bacterial colonisation in the urinary tract and the flushing out of the bacteria via urine.

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wordings for the health claim: "Pacran® helps to inhibit the adhesion of P-fimbriated *E. coli* to the urinary tract cells".

Specific conditions of use as proposed by the applicant

The applicant has proposed an intake of 500 mg/day of Pacran® cranberry powder. It can be administered as 500 mg once a day or 250 mg twice a day. The target population proposed is sexually active women with a history of UTIs.

ASSESSMENT

1. Characterisation of the food

The applicant stated that the food that is the subject of the health claim is Pacran®, which contains cranberry powder obtained from the blend of whole North American cranberries (*Vaccinium macrocarpon*, syn. *V. macrocarpon* Aiton or *V. macrocarpon* L).

The applicant claims that PACs are the main food constituent in Pacran® which are responsible for the claimed effect. The PACs constitute a group of flavan-3-oligomers and polymers. There are differences in the linkages (A- or B-type) between the monomeric units. The A-type linkages are restricted to cranberries and a few other dietary sources. The PAC content and the ratio of PAC type A were specified. In addition to PACs, Pacran® contains other flavonoids such as anthocyanins and flavonols, as well as phenolic acids and non-phenolic organic acids (such as quinic acid, citric acid and malic acid).

Pacran® consists of dried cranberry solids. The content of PAC in the product is measured by 4-dimethylaminocinnamaldehyde (DMAC) colorimetric assay with the use of A2 dimer standard, and the information about PAC content is provided. High-performance liquid chromatography (HPLC) methodology is used for the determination of the content of monomeric PAC components.

Information about the manufacturing process, the stability and the batch-to-batch variability has been provided. The content of flavonoids and non-phenolic organic acids in cranberry can be measured by established methods.

The Panel considers that the food, Pacran®, which is the subject of the health claim is sufficiently characterised in relation to the claimed effect.

2. Relevance of the claimed effect to human health

The claimed effect proposed by the applicant is “helps to inhibit the adhesion of P-fimbriated *E. coli* to the urinary tract cells”. The target population proposed by the applicant is “sexually active women with a history of UTIs”.

Bacterial adherence to mucosal surfaces is facilitated by fimbriae, which are proteinaceous fibres of the bacterial cell wall (Duguid et al., 1955; Beachey, 1981). Preventing adhesion facilitates urinary flushing of the bacteria, and thereby preventing bacterial colonisation of the urinary tract (Foo et al., 2000).

The Panel considers that the health claim refers to defence against bacterial pathogens in the lower urinary tract of healthy women without signs or symptoms of UTI and does not include the treatment of UTI.

The Panel considers that defence against bacterial pathogens in the lower urinary tract is a beneficial physiological effect.

3. Scientific substantiation of the claimed effect

The electronic search tool Dialog was used to access eight literature databases (Medline, Allied and Complementary Medicine, Foodline: Science, CAB Abstracts, Elsevier Biobase, National Technical Information Service, EMBASE and Adis Clinical Trials Insight) with the following keywords: “cranberry” or “*Vaccinium macrocarpon*” or “Pacran”, “urinary tract” or “UTI” or “bladder or kidney or renal infection” or “cystitis” or “pyelonephritis” or “pyuria” or “dysuria” or “polyuria” or “oliguria” or “haematuria” or “anti-adhesion” or “anti-adherence” or “adhesion” or “adherence” or “bacteria pathogen” or “pathogenic microorganism” or “pathogenic organism” or “uropathogen” or “*Escherichia coli*”. The search was limited to randomised intervention studies in humans performed with Pacran®. The applicant added three unpublished studies to the list of pertinent studies.

As a result, the applicant identified four studies as pertinent to the claim: two human intervention studies and two *ex vivo* studies.

The first study (unpublished A, claimed as proprietary) studied the effect of Pacran® on the incidence of UTI in sexually active female subjects with recurrent urinary infections. In this randomised, double-blind, two-arm study, women (aged 18–60 years) who had had at least two episodes of UTI treated with antibiotics over the preceding 12 months were included. Study participants (n = 182) were randomised to take Pacran® 500 mg/day (n = 89) or placebo (n = 93) for six months. The primary outcome measure was the cumulative rate of first occurrence of symptomatic UTI. Secondary outcomes included the proportion of participants experiencing a recurrent UTI in each group, the time to first UTI, the total number of recurrent UTIs experienced, and urinalysis and safety indices (haematology and clinical chemistry parameters). Seventeen women (10 in the Pacran® group and 7 in the placebo group) did not complete the study. The results were presented as intention to treat (ITT) analysis for 176 women (n = 83 in the Pacran® group and n = 93 in the placebo group). Six participants from the Pacran® group were excluded because they were incorrectly enrolled into the study. The reasons given for the incorrect enrolment were that three were younger than 18 years and three had only one episode of UTI in the previous 12 months. The Panel notes that the process of randomisation was not sufficiently described, that so-called ITT analysis was performed including 13

drop-outs but excluding six completers (all allocated to the intervention group) and that protocol deviations were not treated equally (three subjects younger than 18 years were excluded from the statistical analysis while “some” women older than 60 years were not excluded). Upon request by EFSA the applicant provided the study report. The ITT analysis performed in the study report (including six completers initially excluded) did not show statistically significant differences between groups in relation to primary outcome. The Panel considers that this study did not show an effect of Pacran® on defence against bacterial pathogens in the lower urinary tract.

In double-blind, placebo-controlled, parallel, three-arm study, Sengupta et al. (2011) compared the effectiveness of Pacran® given in two doses (500 and 1000 mg/day) for 90 days vs. placebo on reducing the recurrence of symptomatic UTI. A group of 60 women, aged 18–40 years with a history of recurrent UTI and were currently culture positive with mild symptoms of UTI, was enrolled. The women were randomly divided into three groups: Pacran® low dose (500 mg/day, n = 21), Pacran® high dose (1000 mg/day, n = 23) and placebo (n = 16). At the baseline evaluation, and at each visit (taken at day 10, 30, 60 and 90), all participants were assessed for symptoms of UTI, serum biochemistry, haematology, urinalysis and urine culture. Norfloxacin (400 mg twice a day) was given as a rescue medication for severe UTI symptoms. The outcomes measured included the incidence of recurrence, defined as the presence of *E. coli* in urine cultures, severity of symptoms and changes in biochemical and haematological parameters. The primary outcome was not specified. Three subjects from the placebo group were lost immediately after randomisation. The Panel notes many limitations of this study: no equal status in relation to positive culture at baseline (*E. coli* was found in 31 % of participants in the placebo group and 67 % and 74 % in the low-dose and high-dose intervention group, respectively), and the placebo group was not blinded for both study participants and investigators. The Panel also notes that no information was given about validation of questionnaire used for the assessment of symptoms, that power calculation was not presented, and no clarification was provided by the applicant on a request by EFSA for further information. The Panel considers that no conclusions can be drawn from this study for the scientific substantiation of the claim.

The applicant also submitted two *ex vivo* studies (unpublished B and C, claimed as proprietary) in which anti-adhesion activity of human urine from subjects consuming either a 500 mg Pacran® or placebo on uropathogenic P-type *E. coli* was measured. The Panel notes that several health claim applications related to the effects of cranberry products standardised by their PAC content on inhibition of adhesion of *E. coli* to uroepithelial cells by measuring the anti-adherent effects of urine from subjects consuming cranberry products have already been evaluated by EFSA (EFSA, 2009; EFSA NDA Panel, 2011, 2013a, b). However, the studies provided in those applications did not establish that inhibition of the adhesion of *E. coli* to uroepithelial cells demonstrated *ex vivo* predicts the occurrence of a clinically relevant inhibition of the adhesion of *E. coli* to uroepithelial cells in humans.

In weighing the evidence, the Panel considers that the one human study from which conclusions could be drawn for the scientific substantiation of the claim did not show an effect of Pacran® on defence against bacterial pathogens in the lower urinary tract.

The Panel concludes that a cause and effect relationship has not been established between the consumption of Pacran® and defence against bacterial pathogens in the lower urinary tract.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food product, Pacran®, which is the subject of the health claim is sufficiently characterised in relation to the claimed effect.
- The claimed effect is “inhibition of adhesion of *E. coli* to urinary tract cells”. The target population as proposed by the applicant is healthy women complaining from recurrent UTI.

Defence against bacterial pathogens in the lower urinary tract is a beneficial physiological effect.

- A cause and effect relationship has not been established between the consumption of Pacran® and defence against bacterial pathogens in the lower urinary tract.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on Pacran® and defence against bacterial pathogens in the lower urinary tract pursuant to Article 13.5 of Regulation (EC) No 1924/2006 (Claim serial No: 0400_FR). November 2013. Submitted by Naturex SA.

REFERENCES

- Beachey EH, 1981. Bacterial adherence: adhesin-receptor interactions mediating the attachment of bacterial to mucosal surfaces. *Journal of Infectious Diseases*, 143, 325–345.
- Duguid JP, Smith IW, Dempster G and Edmunds PN, 1955. Non-flagellar filamentous appendages (“fimbriae”) and haemagglutinating activity in *Bacterium coli*. *Journal of Pathology and Bacteriology*, 70, 335–348.
- EFSA (European Food Safety Authority), 2009. Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) on a request from Ocean Spray International Services Limited (UK), related to the scientific substantiation of a health claim on Ocean Spray Cranberry Products® and reduced risk of urinary tract infection in women by inhibiting the adhesion of certain bacteria in the urinary tract. *The EFSA Journal* 2009, 943, 1–16.
- EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2011. Scientific Opinion on the substantiation of health claims related to proanthocyanidins from cranberry (*Vaccinium macrocarpon* Aiton) fruit and defence against bacterial pathogens in the lower urinary tract (ID 1841, 2153, 2770, 3328), “powerful protectors of our gums” (ID 1365), and “heart health” (ID 2499) pursuant to Article 13(1) of Regulation (EC) No 1924/2006. *EFSA Journal* 2011;9(6):2215, 18 pp. doi:10.2903/j.efsa.2011.2215
- EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013a. Scientific Opinion on the substantiation of a health claim related to Monurelle® and reduction of bacterial colonisation of the urinary tract by the inhibition of the adhesion of P-fimbriated *E. coli* to uroepithelial cells pursuant to Article 13(5) of Regulation (EC) No 1924/2006. *EFSA Journal* 2013;11(2):3082, 9 pp. doi:10.2903/j.efsa.2013.3082
- EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2013b. Scientific Opinion on the substantiation of a health claim related to proanthocyanidins in Urell® and reduction of bacterial colonisation of the urinary tract by inhibition of the adhesion of P-fimbriated *E. coli* to uroepithelial cells pursuant to Article 13(5) of Regulation (EC) No 1924/2006. *EFSA Journal* 2013;11(7):3326, 10 pp. doi:10.2903/j.efsa.2013.3326
- Foo LY, Lu Y, Howell AB and Vorsa N, 2000. The structure of cranberry proanthocyanidins which inhibit adherence of uropathogenic P-fimbriated *Escherichia coli* in vitro. *Phytochemistry*, 54, 173–181.
- Sengupta K, Alluri KV, Golakoti T, Gottumukkala GV, Raavi J, Kotchrlakota L, Sigalan SC, Dey D, Ghosh S and Chatterjee A, 2011. A randomized, double-blind, controlled, dose dependent clinical trial to evaluate the efficacy of a proanthocyanidin standardized whole cranberry (*Vaccinium macrocarpon*) powder on infections of the urinary tract. *Current Bioactive Compounds*, 7, 1–8.
- Unpublished study, A. A randomized, double-blind, placebo-controlled clinical trial to investigate the efficacy of cranberry fruit powder (Pacran®) in the prevention of recurrent urinary tract infection in women.

Unpublished study, B. Assessment of bacterial anti-adhesion activity of Pacran® in human urine against P-type uropathogenic *Escherichia coli*. A randomized, placebo-controlled, ex vivo, double-blind, crossover trial.

Unpublished study, C. Assessment of bacterial anti-adhesion activity of Pacran® in human urine against P-type uropathogenic *Escherichia coli*. A randomized, placebo-controlled, ex vivo, double-blind, crossover trial.

ABBREVIATIONS

DMAC	4-dimethylaminocinnamaldehyde
HPLC	high-performance liquid chromatography
ITT	intention to treat
PAC	proanthocyanidin
UTI	urinary tract infection